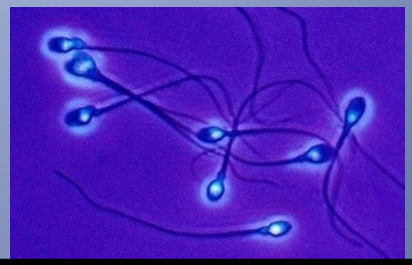
Cryopreservation: Key Performances Indicators

NHS Lothian



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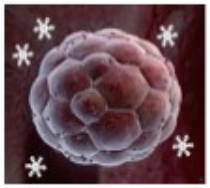

Optimizing Human Gamete and Embryo Freezing

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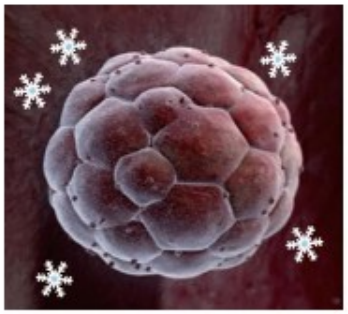
Optimizing Human Gamete and Embryo Freezing



Sede dell'Evento

Sala Convegni
Ordine dei Medici e degli Odontoiatri
della Provincia di Genova
Piazza della Vittoria, 12/4 - Genova

13 giugno 2014

EFREC RIE, Edinburgh

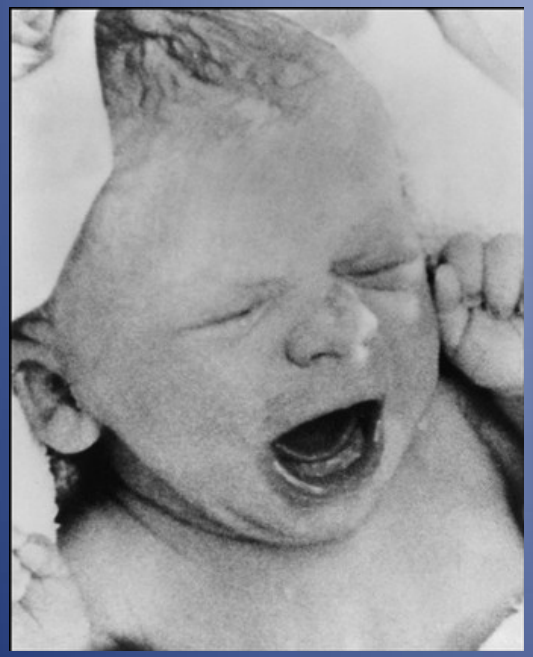
- 1991:First IVF Unit in Scotland
- 1992:First baby born in Scotland(frozen-thaw)
- 2010:First PGD center in Scotland
- 2013:512 retrievals ICSI/ IVF
- 65 PGD Cycles
- 5 embryologists, 5 physicians
- Success rate overall:38% FH. Patient < 37: 54%
- Top 10 IVF unit in UK

Outline

- Key Performance Indicators (KPIs)
- Benchmarks
- Embryology Process Indicators
- KPIs for Cryobanking

PLEASE ASK QUESTIONS!

Introduction

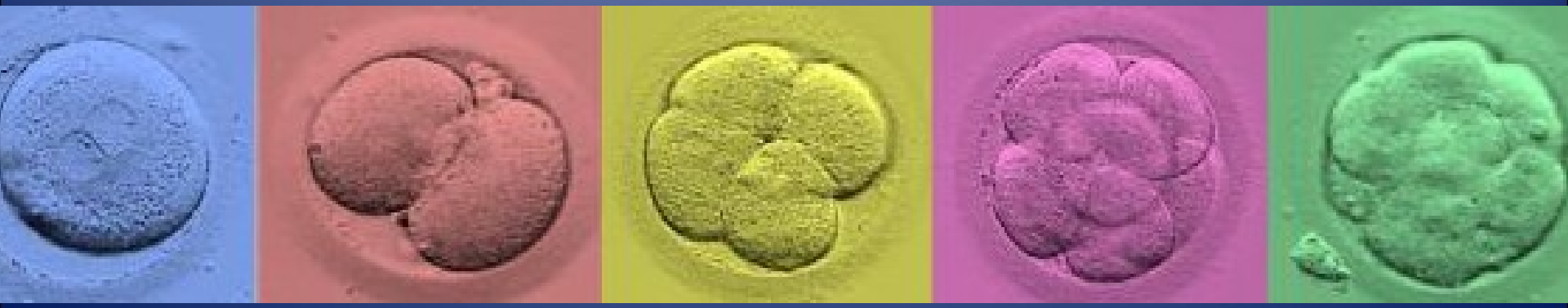


1978 - 2014
Almost 5 million babies have been born after ART (Worldwide)

Research has resulted in the development of more physiological culture media capable of maintaining the viability of the developing embryo.

…but still

IVF technique is still inefficient, as only 10–30% of all embryos replaced in the uterus implant and result in a live baby (Martin JR et al., 2010)



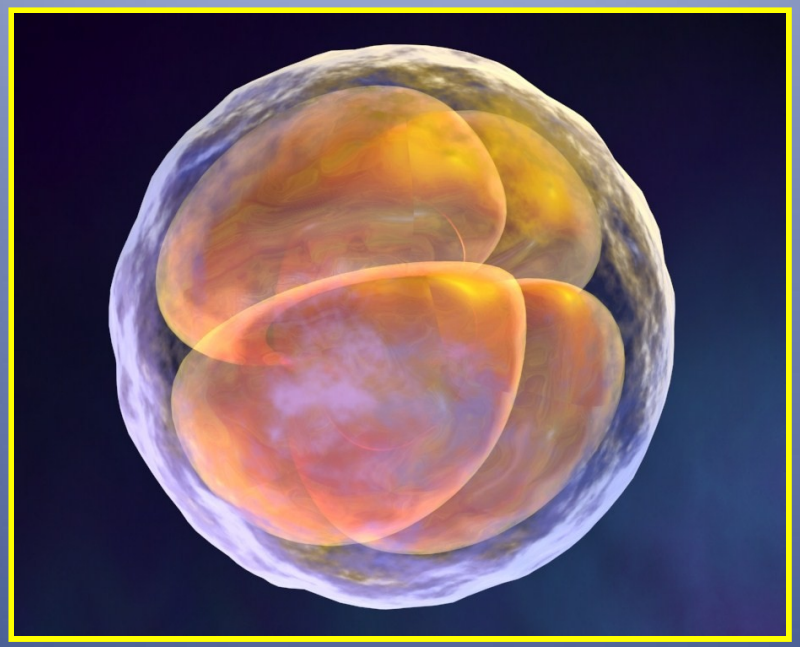
Culture System: In Vitro Stressors

Oxidants

Light

Temperature

pH



Toxins

ROS

VOC

Air Quality

Osmolality

It is crucial to minimize perturbations in the atmosphere around the embryo

The key to success in the IVF laboratory ?

- Dedication and Skilled Staff
- Excellent attention to details
- Adequate Equipment and proper use
- Interaction with clinicians/communication

Quality control and quality management

Indicators and benchmarks

Indicators: Introduction

Indicators: You can’t control what you can’t measure

ISO terminology: Key Performance Indicators (KPIs)

RELIABLE: Measure something useful.
Define the process to be monitored

ROBUST: Measure only the intended process
Minimize extra effects

ROUTINE: Data collection must not be arduous
or a lot of extra work (easy)

“WORK SMARTER NOT HARDER”

Benchmarks: Definition

The continuous process of measuring performance against a strongest competitors or a leader in the field

Definitions

BENCHMARKS:

- What should be achieved if all goes well (Quality Assurance)
- Aspirational value (best practice goal)

KPIs:

- Must reflect your GOALS
- Not necessarily achievable by all Labs
- Aspirational targets for Quality Improvement
- Minimum performance level (basic competency)

KPIs must be comparable:

Require precise definitions and standardized methods for their determination

Key Performance Indicators(KPIs) are used:

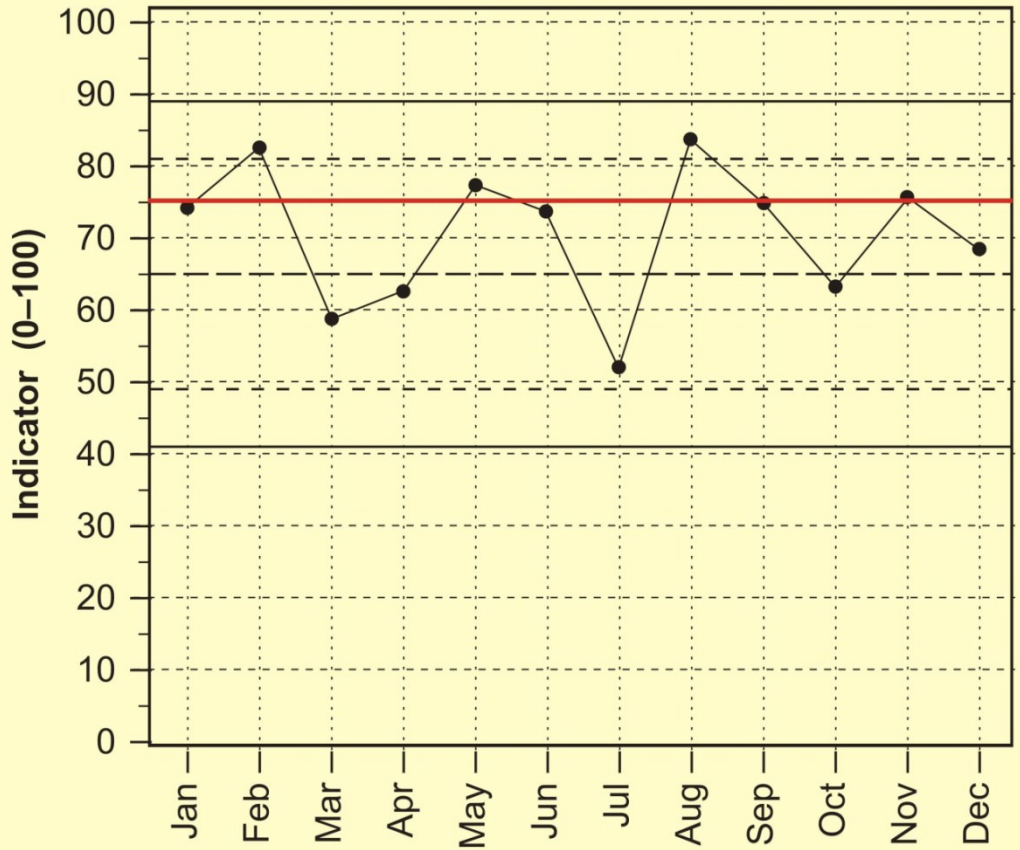
- To evaluate a new technique or process
- As minimum standard for the program as a whole
- To monitor ongoing performance as part a QM system
- For benchmarking and quality improvement

There are no published KPIs for oocyte and embryo cryopreservation

Embryology Process Indicators

	IVF	ICSI
LABORATORY	% mature COCs at OPU	% (mature) MIIs after stripping
	Fertilization rate (≥2PNs)	Damage rate during ICSI
	Normal fertilization rate (2PNs)	Degeneration rate on Day 1
	Low or failed fertilization rate	Normal fertilization rate (2PNs)
	Zygote cleavage rate	Zygote cleavage rate
	Day 2 embryo development rate (assess at 44 ± 1 h)	
	Day 3 embryo development rate (assess at 68 ± 1 h)	
	% good or better embryos on Day 3	
	Day 5 blastocyst development rate (assess at 116 ± 2 h)	
	Utilization rate (embryos suitable for ET or cryopreservation)	
CLINIC	Positive pregnancy test (+ve ßhCG)	
	Implantation rate per embryo transferred	
	Clinical pregnancy rate (fetal heart per ET)	

The Process Control ("Chat")



Upper control limit

Upper warning limit

Target value ("benchmark")

Control mean

Lower warning limit

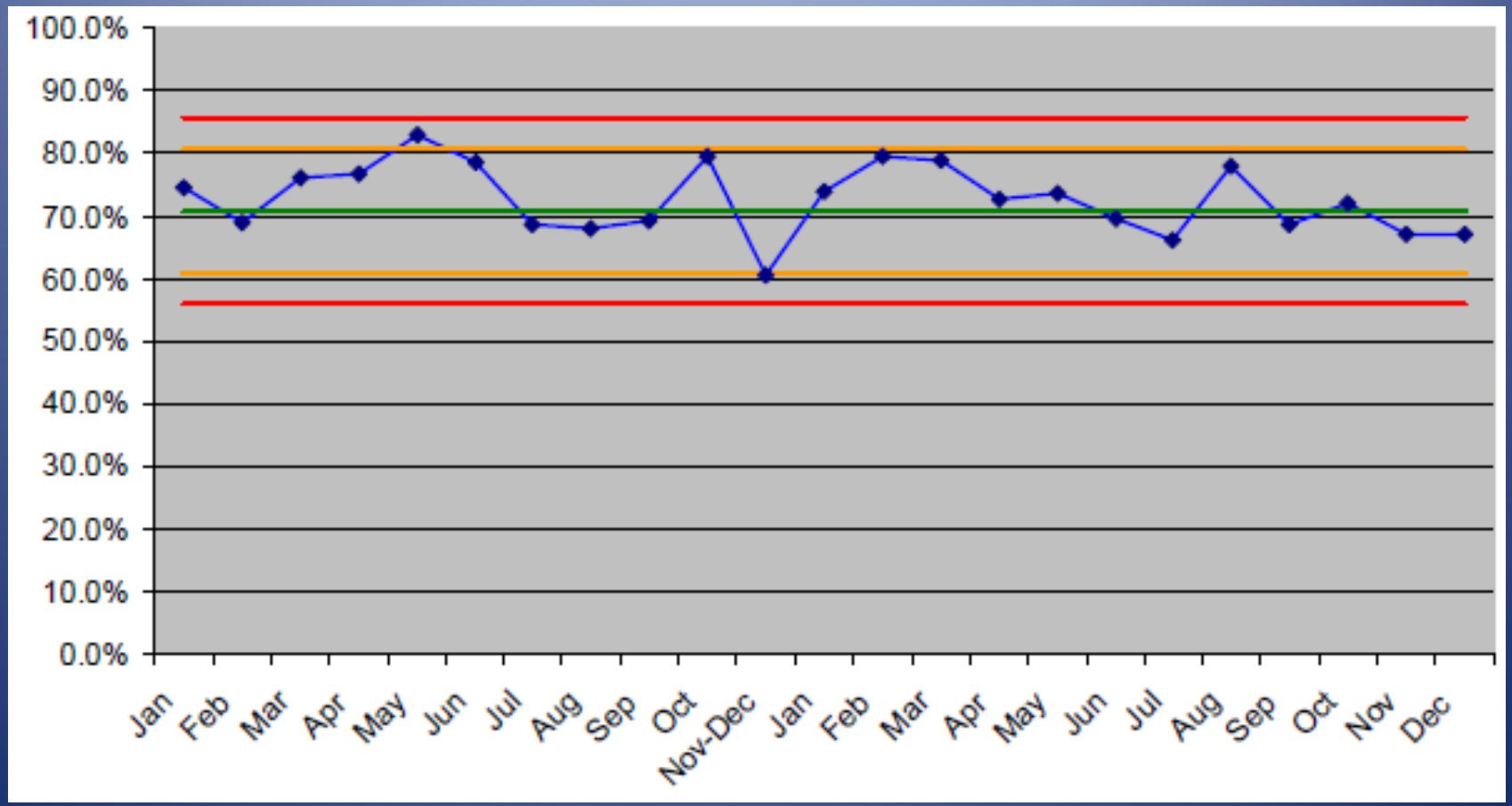
Lower control limit

Control limits = mean ± 3SD

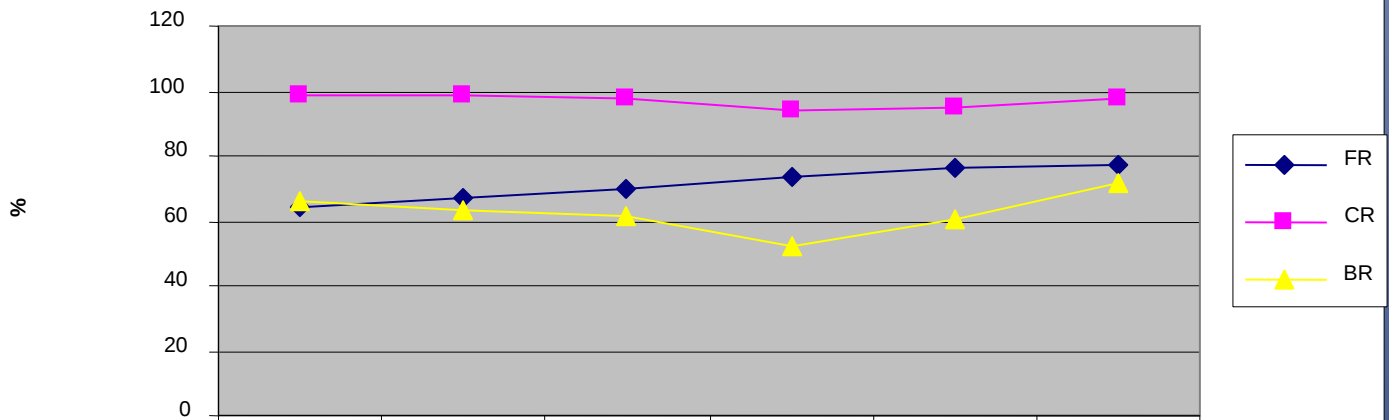
Warning limits = mean ± 2SD

IVF Fertilization Rate

2PNs as % of oocytes inseminated



IVF Embryology KPI



	J	F	M	A	M	Ju
FR	64.5	66.7	69.60	73.4	76.7	77
CR	98.3	98.6	98	94.1	95.3	97.8
BR	65.9	62.9	61	52.1	60.7	72

Triggers for action:

FR <60% CR <90% Blast Rate <40%

KPIs for Cryobanking

For gamete and embryo cryobanking: all commonly used KPIs related to cryosurvival

- Assessed immediately post-thawing or post-warming
- Evaluated through normal function or development after thawing or warming

Cryobanking:Terminology

- **Cryopreservation(“slow freezing”):**

  Freezing “frozen”

  Thawing “post-thaw”

- **Vitrification:**

  Cooling “vitrified”

  Warming [not *devitrification**]“post-warming”

Sperm Freezing KPIs

Process measures:

- Sperm concentration in accordance with the dilution ratio

- Timing of process steps

- Average number of units frozen per ejaculate

Cryosurvival:

Post-thaw assessment of semen / sperm specimens; generally-accepted values are:

- Sperm motility reduced by no more than 50%

Oocyte-Zygote-Embryo Cryo KPIs

No generally-accepted benchmarks are available

Even within the basic cryopreservation approaches, exist numerous sources of variability

- Biological: patients, stimulations, workstations, lab and culture systems
- Cryo / vitrification media formulations
- Processing protocols
- Packaging devices
- Cooling / vitrification methods / protocols
- Thawing / warming methods / protocols

ALPHA:Scientists in Reproductive Medicine

Reproductive BioMedicine Online (2012) 25, 146–167

ELSEVIER

www.sciencedirect.com
www.rbmonline.com

ARTICLE

The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting

Oocyte Cryo KPIs

- % of oocytes that appear intact post-cryo:
  ≥ 75%

- Fertilization rate per post-cryooocyte, using ICSI: ≥ 65% (same as for fresh oocytes)

- Cleavage rate per fertilized post-cryooocyte:
  ≥ 95% (same as for fresh oocyte zygotes)

Embryo Cryo KPIs:Zygotes

- % of zygotes that appear intact post-cryo:
  ≥ *90%*

- % of post-cryo zygotes that cleave:
  ≥ *95% (same as for fresh zygotes)*

Cleavage Stage Embryo Cryo

Main factors that predict cryosurvival:

- Fragmentation
- Uneven cell number
- Dark, granular cytoplasm
- No / minimal fragmentation
- Even cell number
- “Good” cytoplasm, “shiny” membranes

But what about embryo developmental competence?

Embryo Cryo KPIs:Cleavage Stages

- % of embryos with at least 50% cells intact post-cryo: ≥ 80%
- % of embryos with all blastomeres intact post-cryo: ≥ 50%
- % of post-cryo embryos that cleave during overnight culture pre-ET: ≥ 75%
- Implantation rate per post-cryo embryo women < 38 years: ≥ 20%

Blastocyst Cryopreservation

"GOOD" blastocysts show better cryosurvival and subsequent developmental competence

- Always Day 5 blastocysts? Or Day 6?
- Optimum criteria to select blastocysts for freezing?
- Early Blast? Expanding blastocysts?
- Expanded blastocysts?
- Laser to Collapse?

IVF Labs use different methods and procedures for assessing embryos

Embryo Cryo KPIs:Blastocysts

- % of blastocysts that are more-or-less intact post-cryo: ≥ *80%*

- % of blastocysts that re-expand within 3 h post-cryo: ≥ *50%*

- % of early blastocysts that expand during overnight culture pre-ET: ≥ *75%*

- Implantation rate per post-cryo embryo women < 38 years): ≥ *30%*

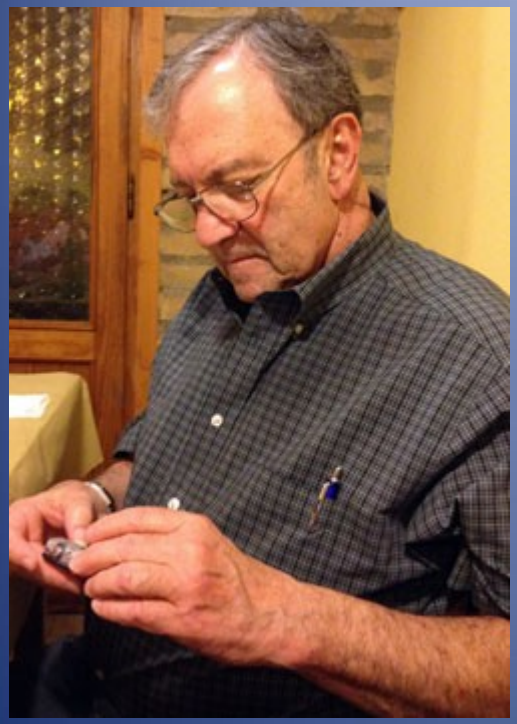
CONSIDERATIONS

- The full exact cryo protocol, including denudation timing and method (for oocytes) should be considered
- Insufficient general experience with Day 4 cryo to support KPI development
- Endometrial preparation issues were not analyzed
- All of the recommended KPIs are for cases that do not include manipulation for PGD

CONCLUSION

- Cryo KPIs must reference Centre-specific fresh KPIs, as there are no international KPIs for fresh IVF/ICSI
- KPIs must always be considered within each Centre’s own Quality Management system
- Standardization of protocol details and training are essential for meaningful KPIs

In Memoriam:Professor Stanley Leibo



- Stanley Leibo passed away on March 25th at the age of 77 following a battle with melanoma cancer.

- Leibo has been a pioneering researcher in cryobiology

- In 1972, working with D.Whittingham and P. Mazur, Leibo freeze successfully for the first time mouse embryos. Millions of children and live animals have since been produced from cryopreserved embryos

In 2009 Leibo was honored with the Pioneer Award from the International Embryo Transfer Society: was described as "indisputably one of the best, and best known, cryobiologists."

Thanks for your attention

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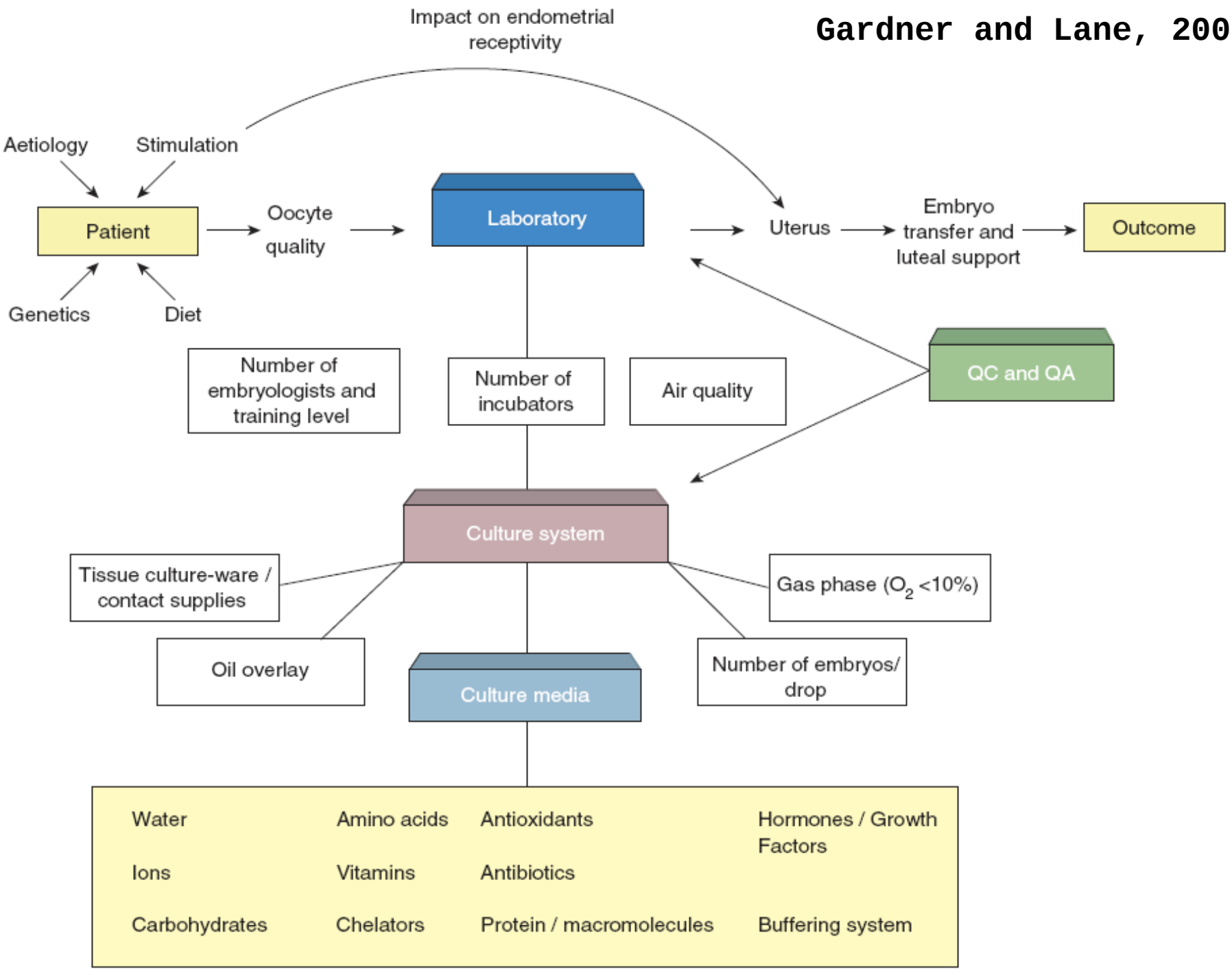
Gardner and Lane, 2008



Which Embryos to Freeze or Transfer

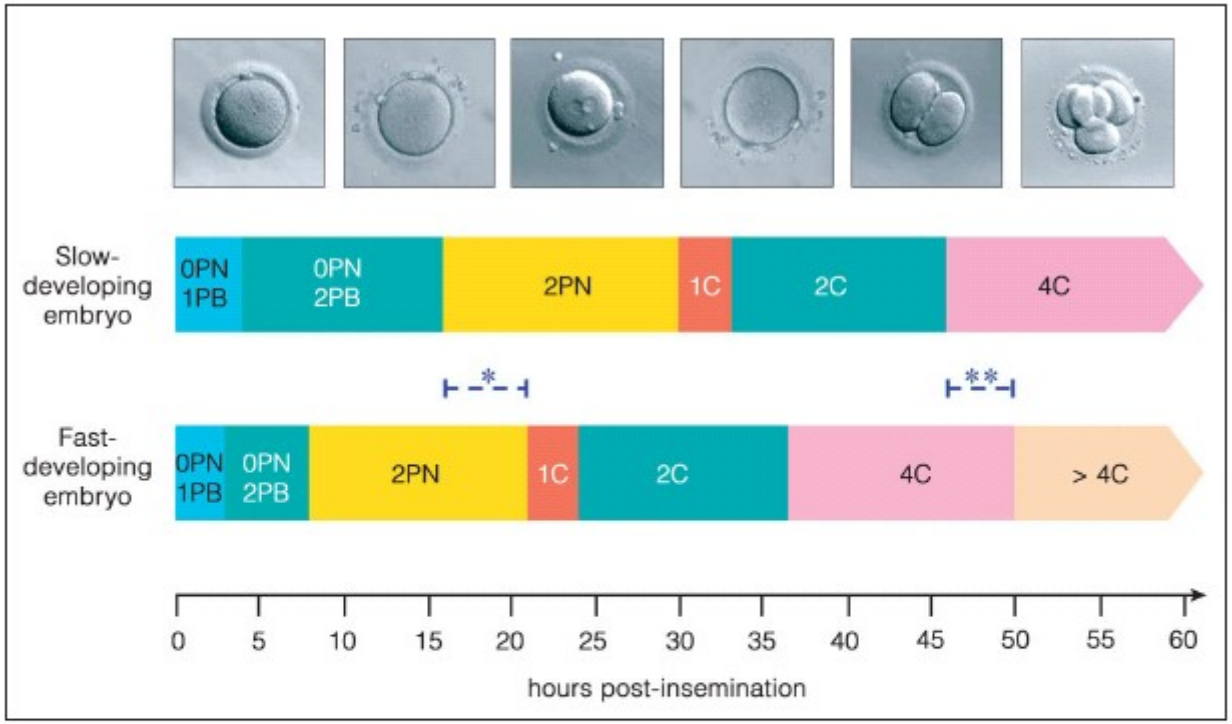


Figure 2. Comparison of the development of slow- and fast-cleaving embryos from fertilisation to the 4-cell stage. Pronuclear breakdown and first cleavage occur earlier in faster-developing embryos than in those with slow development. The time-span between the development of faster- and slower-developing embryos can be up to 8–12 hours. It can easily occur that faster- and slower-developing embryos have the same number of blastomeres at the time of morphological assessment performed before embryo transfer.

0PN = no pronucleus; 2PN = two pronuclei; 1PB = one polar body; 2PB = two polar bodies; 1C, 2C, 4C = 1-, 2- and 4-cell stage of the embryo; *Too early assessment of pronuclear breakdown does not help to distinguish early- and late-developing embryos. **Morphological assessment in the indicated period does not allow differentiation of early- and late-developing embryos. Assessment of early pronuclear breakdown or early cleavage can help to determine viability in case of embryos with similar morphological characteristics. [Author permission granted by P. Fancsovits]